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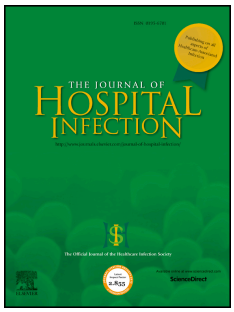

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Clostridium difficile classification overestimates hospital acquired infections

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Abbreviated/Running title: Classifying *C. difficile* infections

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Summary

Background: *Clostridium difficile* infections are common among hospitalised patients, with some infections acquired in hospital and others in the community. International guidelines classify cases as hospital-acquired if symptom onset occurs >2 days after admission. This classification informs surveillance and infection control, but has not been verified by empirical or modelling studies.

Aims: To assess current classification of *C. difficile* acquisition using a simulation model as a gold standard.

Methods: We simulated *C. difficile* transmission in a range of hospital scenarios. We calculated the sensitivity, specificity and precision of classifications that use cut-offs ranging from 0.25 hours to 40 days. We identified the *optimal* cut-off that correctly estimated the proportion of cases that were hospital acquired and the *balanced* cut-off that had equal sensitivity and specificity.

Findings: The recommended two-day cut-off overestimated the incidence of hospital-acquired cases in all scenarios and by >100% in the base scenario. The two-day cut-off had good sensitivity (96%) but poor specificity (48%) and precision (52%) to identify cases acquired during the current hospitalisation. A five-day cut-off was balanced and a six-day cut-off was optimal in the base scenario. The optimal and balanced cut-offs were more than two days for nearly all scenarios considered (ranges four to nine days and two to eight days).

Conclusions: Current guidelines for classifying *C. difficile* infections overestimate the proportion of cases acquired in hospital in all model scenarios. To reduce misclassification bias, an infection should be classified as being acquired prior to admission if symptoms begin within five days of admission.

Keywords: *Clostridium difficile;* hospital acquired infections; surveillance definitions; mathematical model.

Introduction

Since *Clostridium difficile* was identified as the causative agent for pseudomembranous colitis in the late 1970s [1], awareness of the pathogen has grown, as has the burden of disease [2]. In 2011, there were an estimated 453,000 *C. difficile* infections (CDIs) and 29,300 deaths in the United States of America alone [3]. Today *C. difficile* is implicated as the cause of 71% of hospital-associated gastrointestinal infections [4].

Most CDI cases are observed in healthcare facilities, but there is increasing recognition of community acquired cases [5]. Symptomatic individuals have mild to severe diarrhoea but patients may also carry the pathogen asymptomatically for weeks or months [6,7]. Because of the potentially long incubation period [8], patients displaying symptoms for the first time in a healthcare facility may have acquired the pathogen prior to admission, obscuring the source of transmission.

The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) have published recommendations for classification of CDIs [9] (Figure 1). They recommend that CDIs with onset of symptoms more than two days after admission to a healthcare facility but prior to discharge be classified as healthcare facility-onset, healthcare facility-associated infections. The recommendation is not evidence-based, but intended to be used as a standard for comparison between healthcare facilities and systems. The classification (or a minor variant) is used to estimate the relative contribution of hospital and community based transmission [3,10], report temporal changes in incidence [11], compare the incidence of hospital-acquired cases before and after interventions [12], and as a case definition for studies comparing hospital-acquired and community-acquired cases [10]. Therefore, it is important that the classification is fit for purpose, i.e. correctly estimates the number of cases that are hospital or community acquired and/or sufficiently discriminates between the two groups.

Individuals may be colonised with *C. difficile* for longer than two days before showing symptoms. One study found the median incubation period was 19 days [13]. Another found that the first quartile and median delays from admission to onset of symptoms were eight days and 17 days respectively [10]. We hypothesise that increasing the cut-off beyond two days will reduce sensitivity, but greatly improve specificity to identify hospital onset, healthcare facility associated CDI.

We modelled *C. difficile* transmission in a healthcare setting to simulate the interaction of pathogen and patient from admission through to discharge. The model has been previously shown to reproduce hospital-level outcomes such as the proportions of infections occurring within 72 hours of admission [14]. We use this model to assess the current guidance for CDI and identify potential improvements to the method of classification.

Methods

Mathematical Model

A detailed description of the model can be found elsewhere [14]. Briefly, we used a stochastic compartmental model of *C. difficile* transmission in a hospital. The model divides admitted patients into fifteen compartments based on immune responses to *C. difficile* toxins (immune, naïve or immunocompromised), *C. difficile* colonisation status (negative, colonised or overgrowth with substantial toxin load) and the status of commensal gut flora (normal or disturbed). Our model simulates the time-course of hospitalised individuals, capturing their state from admission to discharge, including exposure to antimicrobials, colonisation with *C. difficile*, onset of CDI, treatment and development of immune responses (Figure 2). We considered settings where mean incidence of CDI is constant and therefore we assumed a constant force of colonisation, allowing us to use the individual Markov chain approximation described in previous work [14] to classify CDI origin. This allowed us to estimate the probability distribution of patient outcomes at the individual level (e.g. probability that a patient colonised at admission did not develop symptoms within two days of admission, but did develop symptoms prior to discharge) without running individual-based simulations.

Case definitions for origin of infection

Though our model simulates recurrent CDI, we considered only the first period of CDI experienced by patients during their hospitalisation. All estimates of incidence and classification were performed for this first CDI episode only. The scope of our model was limited to hospitalised patients so we could not consider any periods of CDI preceding or following the simulated hospitalisation. We therefore were unable to assess the classification of patients by history of recent hospitalisation and instead focused on events occurring during a single hospitalisation. An infection was considered *previously acquired* (PA-CDI) if the patient was colonised at admission and was continuously colonised until the onset of symptoms, including where patients had symptoms on admission. This definition necessarily included all community-acquired cases, but also included cases where the infection was acquired during a previous hospitalisation. All other CDIs were considered *hospital acquired in the current hospitalisation* (HACH-CDI). This included CDIs where the patient was not colonised at admission and CDIs where the patient cleared their initial colonisation and was re-colonised in hospital prior to the onset of symptoms. We used these definitions and our model to calculate the distribution of time between admission and onset of symptoms for HACH-CDI and PA-CDI.

Assessing the classification of origin of infection by time since admission

We assessed the classification of cases using the time between admission and onset of symptoms, emulating the first step in the IDSA and SHEA recommendations (Figure 1). For a two-day cut-off, all CDIs with onset of symptoms before the cut-off were classified as PA-CDI, with all remaining CDIs classified as HACH-CDI. We calculated the incidence of

CDIs classified as HACH-CDI or PA-CDI and the proportions of these that were correctly and incorrectly classified by comparison to the true history of individuals in the model. To identify potential improvements to the classification, we repeated this process for different cut-off times from 0.01 to 40 days.

It is common to design binary classification systems so that they balance sensitivity (the proportion of 'positives' correctly classified) and specificity (the proportion of 'negatives' correctly classified). We identified the cut-off that achieves this and called it the 'balanced' cut-off. However, such classifications misclassify larger numbers of individuals from the majority class than from the minority class, overestimating the incidence of the latter. Therefore, we also determined the 'optimal' cut-off time that balanced sensitivity with precision (the proportion of individuals classified 'positive' that are actually 'positive'). Using this cut-off there was one incorrectly classified PA-CDI for each incorrectly classified HACH-CDI, and the total numbers of cases classified as either HACH-CDI or PA-CDI were equal to the true numbers of HACH-CDI or PA-CDI cases.

To determine whether PA-CDI and HACH-CDI cases could be differentiated by the time from admission to onset of symptoms, we calculated the concordance probability, which is the probability that the time since admission to onset of symptoms would be greater in a randomly chosen HACH-CDI than a randomly chosen PA-CDI.

Sensitivity Analysis

The parameter values for the base scenario, which reflected a moderate CDI incidence setting, was chosen based on previous work [14]. Sensitivity analysis has shown that the two most influential parameters are those governing the person-to-person transmission rate and the mean length of stay for patients admitted overnight. In addition, the proportion colonised at admission and the mean time for *C. difficile* overgrowth to occur in colonised patients with disturbed gut flora were identified as factors likely to have a significant impact on incidence or the time-course of infection and therefore affect the classification of CDIs. We calculated the balanced and the optimal cut-off times and the concordance probability, varying each of these parameters independently.

Results

In the base scenario, the recommended two-day cut-off had good sensitivity but poor specificity to identify CDI acquired in the current hospitalisation (Figure 3), overestimating the proportion of CDIs acquired in the current hospitalisation by nearly 100% (Figure 4). Longer cut-offs decreased the sensitivity but increased specificity to identify CDI acquired in the current hospitalisation. A five-day cut-off was balanced and a six-day cut-off was optimal (Figure 3).

Symptom onset for previously acquired cases was generally closer to the time of admission than cases acquired during the current hospitalisation. The concordance probability – the probability that the time from admission to onset of symptoms was

shorter in a random previously acquired CDI than in a random CDI acquired in the current hospitalisation – was 0.842 in the base scenario. This result was insensitive to the assumptions about the hospital setting, falling between 0.83 and 0.88 for all parameter values considered in the sensitivity analysis (Supp. Figure 1)

The optimal and balanced cut-off times depended on the characteristics of the hospital setting and our assumption about the rate at which *C. difficile* overgrowth occurs in colonised patients (Figure 5). In our sensitivity analysis, the optimal cut-off time was most sensitive to the person-to-person transmission rate while the balanced cut-off time was most sensitive to the mean length of stay. Both the optimal and balanced cut-offs were somewhat sensitive to the mean time to *C. difficile* overgrowth. The optimal cut-off was longest in settings with little person-to-person transmission, while the balanced cut-off was longest in settings with longer mean length of stay. Both the optimal and balanced cut-offs were longer when *C. difficile* overgrowth was assumed to develop more slowly.

A two-day cut-off was not optimal for any of the scenarios considered. No cut-off time was optimal for all scenarios; however some cut-offs resulted in only moderate over- or under-estimation of for a wide range of parameters (Figure 5). A cut-off of approximately 5.5 days did not overestimate or underestimate incidence of hospital acquired or previously acquired CDI by more than 20% for a wide range of mean times to *C. difficile* overgrowth (1-9 days), proportion colonised at admission (0.1-15%), mean length of stay (3-16 days) and rate of person-to-person transmission (0.075-0.14). In our sensitivity analysis, the scenario with the shortest optimal cut-off (3.6 days) was the scenario with very high person-to-person transmission (0.18). This extreme scenario had double the person-to-person transmission of the base scenario, and resulted in 45 hospital-acquired CDIs per 10,000 patient-days.

The classification error of a two-day cut-off was much higher in settings with less person-to-person transmission and substantially higher in settings with shorter mean length of stay (Supp. Figure 2). If transmission was set to 33% of the base rate, a two-day cut-off overestimated the incidence of CDI acquired in the current hospitalisation by over 350%. Even a six-day cut-off overestimated the incidence by 100% in this low-transmission setting. However the balanced cut-off was only slightly higher in a low incidence setting (5.0 days) than in a high incidence setting (4.9 days).

Discussion

Time from admission to onset of symptoms is a reasonable measure for discriminating CDIs acquired in the current hospitalisation from previously acquired CDIs. IDSA and SHEA recommend a cut-off of two days for the classification of hospital onset CDIs as community or hospital acquired. This cut-off systematically overestimates the proportion of CDIs that are acquired in the current hospitalisation and underestimates the proportion that is acquired prior to admission. Since all community acquired CDIs observed in healthcare settings must be acquired prior to admission, the current

guidelines may also systematically underestimate the proportion of cases that are community acquired. Moreover, the low specificity of the two-day cut-off for identifying hospital acquired cases may cause significant misclassification bias in studies that compare hospital and community acquired cases, reducing apparent differences between the two groups.

Since our model did not differentiate strains of *C. difficile,* our definition of previously acquired CDI does not exclude patients that were colonised at admission but subsequently acquired an additional strain of *C. difficile* prior to the onset of symptoms. This is unlikely to represent a significant portion of previously acquired CDIs [15] and so is unlikely to affect our recommendations. The structure and parameter values in our model synthesises the peer review literature on hospital associated CDIs [14], and is not fitted to a single data set. However, our key finding, that the standard classification of CDIs overestimates the proportion of cases acquired in the current hospitalisation, is robust to very large variations in all parameters.

There is a large variation in mean hospital length-of-stay worldwide. Within the OECD, mean lengths of stay range between 3.9 days (Turkey) and 17.2 days (Japan) [16]. Our recommended optimal cut-off is sensitive to the mean length of stay but a cut-off of five days performs well over this entire range. In contrast, a cut-off of two days consistently overestimates the incidence of CDI acquired in the current hospitalisation and overestimates the incidence of CDI acquired in the current hospitalisation by more than 100% when the mean length of stay is less than six days.

The rate of person-to-person transmission is difficult to measure directly and is likely to vary significantly between settings due to differences in hygiene protocols and adherence to these protocols. The degree of person-to-person transmission in our base scenario was estimated from hospitals with high incidence of CDI (28.1 cases per 10,000 patient days) [14,17], and therefore may lie in the upper end of the plausible range. The optimal cut-off is longer in settings with less person-to-person transmission. Therefore, in many settings – especially those that have effective infection control programs – an even longer cut-off may be required to avoid overestimating the incidence of CDI acquired in the current hospitalisation. Since it is not usually possible to estimate the rate of person-to-person transmission without knowing the incidence of hospital acquired infection and colonisation, and most estimates of the incidence of hospital acquired cases are based on the very classification scheme we are assessing, in practice we cannot calculate the optimal cut-off for a given setting. However, a five-day cut-off balances sensitivity and specificity independent of the rate of person-to-person transmission and is approximately optimal for a range of transmission rates.

IDSA and SHEA also recommend that only those cases arising >84 days (12 weeks) after the most recent hospital discharge should be classified as community acquired [9]. This recommendation may also lead to systematic misclassification, with the extent of misclassification determined by the choice of cut-off. However, the scope of our model was limited to hospitalised patients so we could not consider any periods of CDI or asymptomatic colonisation preceding or following simulated hospitalisations. Therefore we are unable to make recommendations for the optimal use of a patient's history of

hospitalisation to classify the origin of CDI for either community onset or hospital onset CDI. This classification should also be assessed with empirical studies or models that simulate patients in communities and hospitals.

It is difficult to determine the source of transmission for CDI cases, and so assess classification by time since admission empirically. Since the same strains of ***C.*** *difficile* circulate in hospitals and communities, cases cannot be distinguished by strain type alone [18,19]. Whole genome sequencing can identify transmission events, but the most comprehensive studies have not sequenced isolates from many asymptomatic carriers, and have not been able to identify a transmission source for ≥75% of all infections [8,18]. Screening all admissions for asymptomatic colonisation, coupled with contact precautions and antimicrobial stewardship for colonised patients, may reduce the incidence of CDI [12,20]. Consequently, studies where screening has occurred may not be representative and thus unsuitable for assessing classification of the origin of infections in settings without screening. Therefore, modelling based approaches may be the best means for assessing the classification of CDIs.

Our findings add to a growing body of evidence that suggests transmission and reservoirs of *C. difficile* outside hospitals are as least as important as within-hospital transmission. Detailed surveillance has found the same strains circulating in communities and hospitals, demonstrating the interconnectedness of the two populations [18,19]. Further, modelling studies have shown the reproduction number (the number of secondary colonisations arising from a typical primary colonisation in a population of susceptible individuals) is less than one in many healthcare settings, suggesting that CDI is sustained primarily by the admission of colonised individuals, not within-hospital transmission [14,21]. Moreover, only 19% [18] of all CDIs and 25% [8] of CDIs in hospitals can be reasonably attributed to transmission from symptomatic inpatients, with the remainder acquired from asymptomatic carriers or sources in the community. While hospital onset CDIs are carefully monitored and reported, community onset CDIs are likely to be underreported – especially in patients who have not been hospitalised recently [22,23].

Standardised definitions and reporting of hospital acquired *C. difficile* infections have value, but the current two-day cut-off is not based on strong evidence and overestimates the proportion of cases acquired during the current hospitalisation. Though it may be difficult to change reporting standards, adopting a five-day or six-day cut-off will improve the classification of potential sources of infection for *C. difficile*, recognising the key role of CDI acquired prior to hospital admission, including community-acquired cases.

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Figures

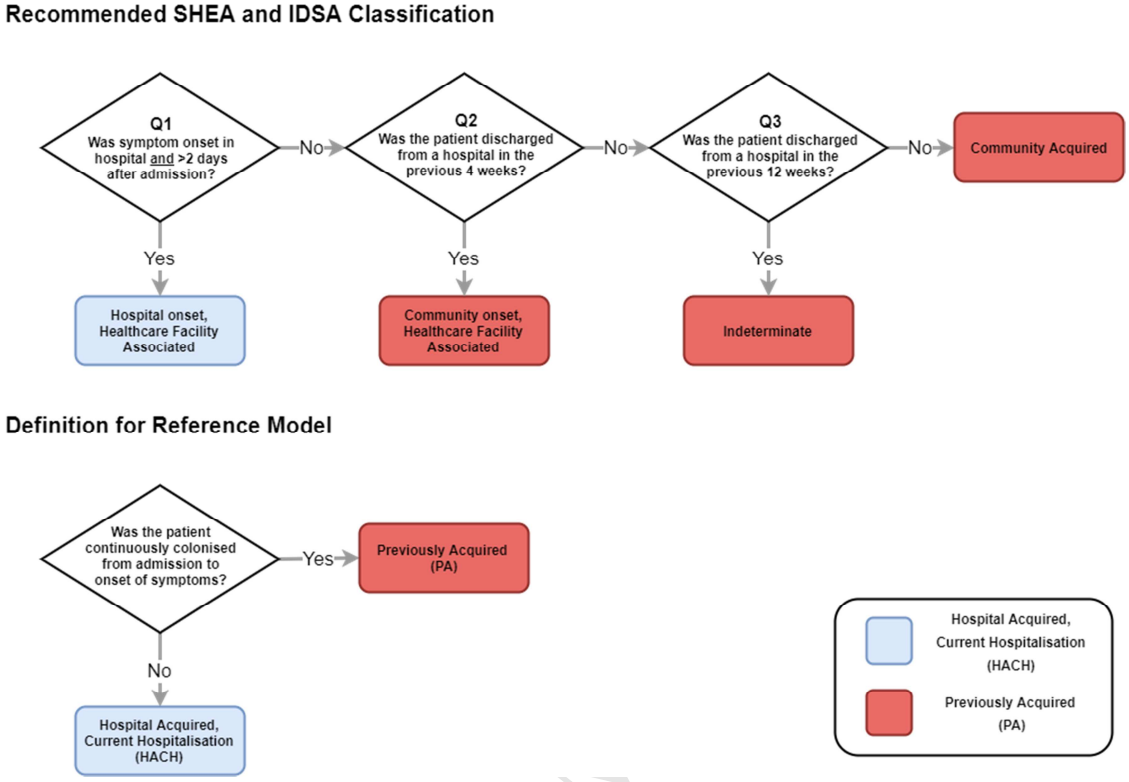

Figure 1

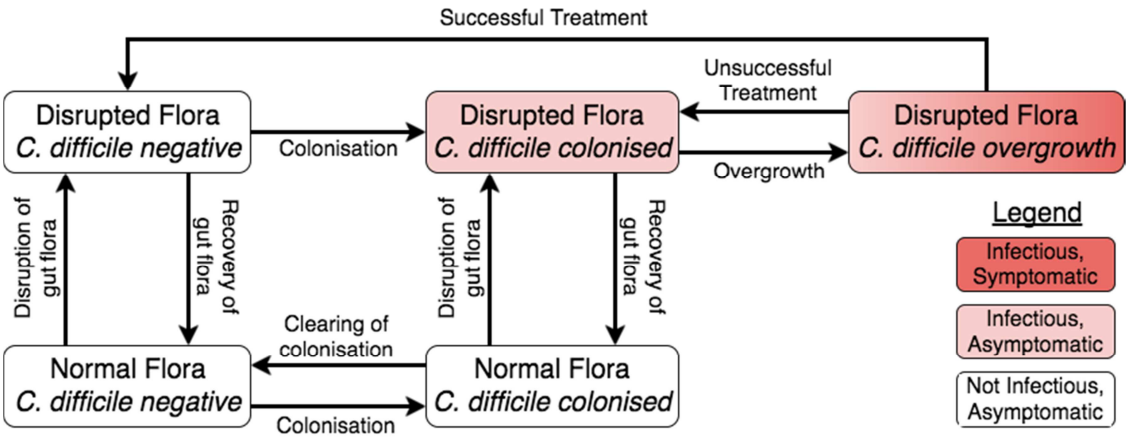

Figure 2

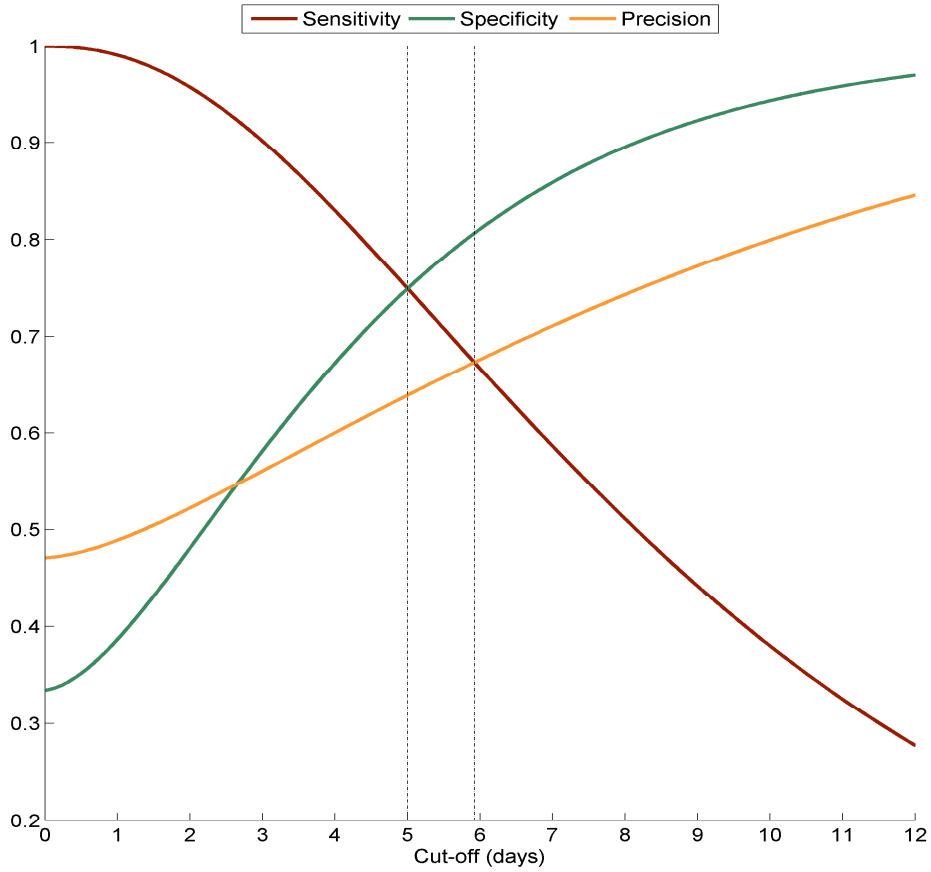

Figure 3

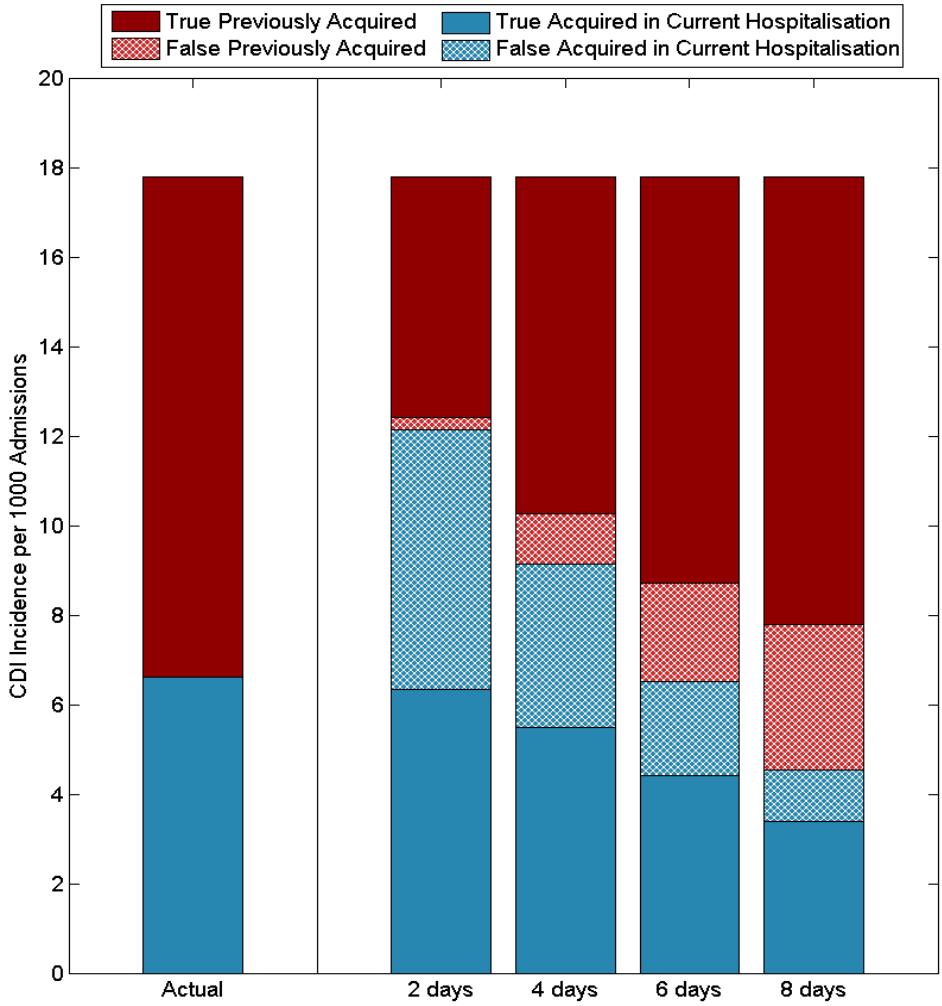

Figure 4

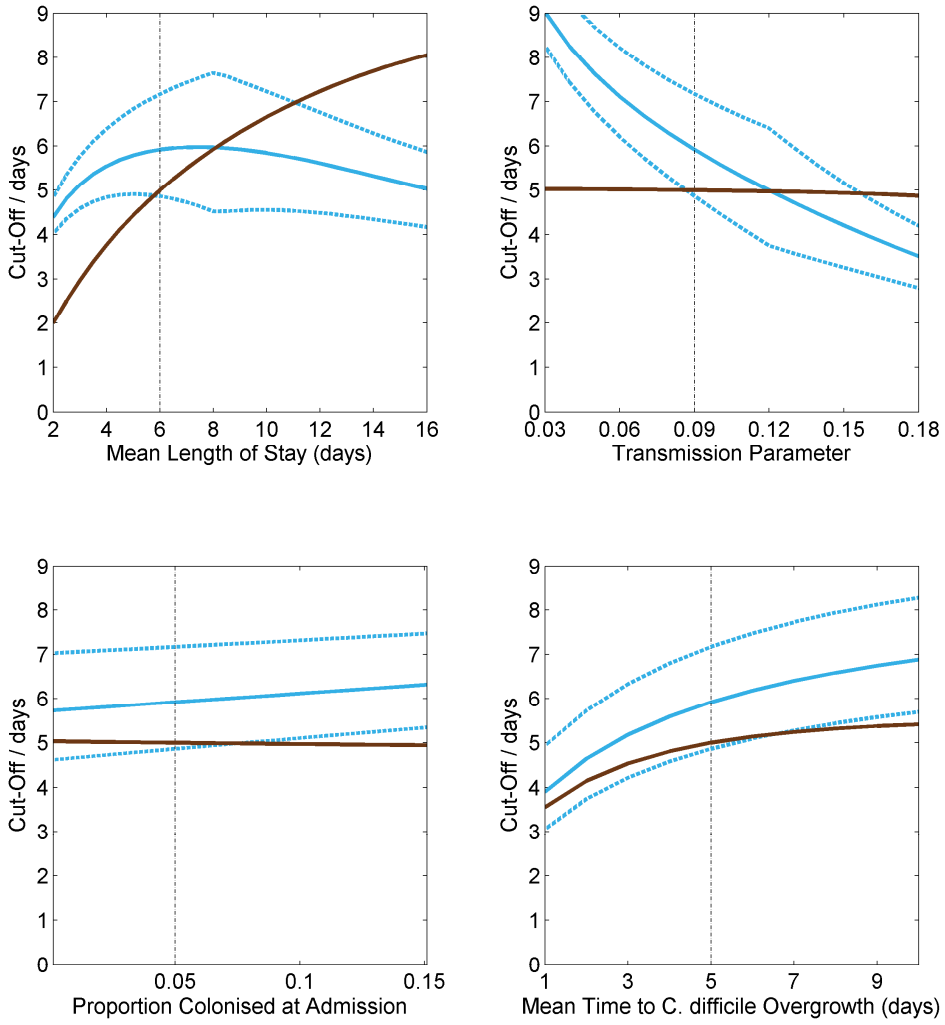

Figure 5

Figure Captions

Figure 1 Classification of CDIs recommended by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) with a comparison to the definitions of previously acquired (PA) and hospital acquired in current hospitalisation (HACH) used in the model.

Figure 2 Diagram summarising the main states and events simulated in the model. Admitted patients can be in any of the above states, and may change states throughout their hospitalisation. Each of the five states is further divided according immunity to *C. difficile* toxins. Only patients with disrupted intestinal flora and *C. difficile* overgrowth but no immunity to toxins are symptomatic for CDI, however all *C. difficile* positive patients with disrupted intestinal flora are infectious.

Figure 3 Sensitivity, specificity and precision of identifying CDIs acquired in the current hospitalisation by time since admission. Results are shown for the base scenario only. Sensitivity and specificity are equal with a five-day cut-off. The optimal cut-off (equal sensitivity and precision) is longer at 5.9 days.

Figure 4 Classification of the origin of CDI by time since admission for selected cut-offs, in the base scenario. Shorter cut-offs detect most cases acquired in the current hospitalisation but misclassify many previously acquired cases, overestimating the proportion of CDIs that are acquired in the current hospitalisation. A cut-off of six days overestimates neither.

Figure 5 The effect of four parameters on the optimal (light blue – equal sensitivity and precision) and balanced (brown – equal sensitivity and specificity) cut-off times for classifying the origin of CDI by time since admission to onset of symptoms. Light blue dashed curves indicate range of cut-offs that over/underestimate the incidence of previously acquired CDIs and CDIs acquired in the current hospitalisation by ≤20%. The vertical dashed lines mark the values of the parameters in the base scenario.